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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/909,796	07/23/2001	Catherine Taylor	10799/13	2704

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EXAMINER	
SCHULTZ, JAMES	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/909,796	TAYLOR ET AL.	
	Examiner	Art Unit	
	J. Douglas Schultz	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,11 and 87-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11 and 87-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

1. Applicant's responses filed January 8, 2004 and November 12, 2003 have been considered. The amendment filed November 12, 2003 has been entered in full. Rejections and/or objections not reiterated from the previous office action mailed August 12, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submissions filed on January 8, 2004 and November 12, 2003 have been entered.

Claim Rejections - 35 USC § 112

4. Claims 1, 11, and 87-89 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to methods of delaying apoptosis in a cell, comprising administering any agent that reduces activation of apoptosis induced eIF-5A, wherein said reduction results in delaying apoptosis. Dependent claims are drawn to specific agents that inhibit eIF-5A activation.

To satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. Thus, an applicant complies with the written-description requirement by describing the invention, with all its claimed limitations, and by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical, structure/function correlation, methods of making the claimed product, and any combination thereof.

In this case, applicants claim language is broadly drawn to methods of inhibiting any apoptosis-induced eIF-5A molecule. Applicants have disclosed a single rat eIF-5A molecule, depicted at SEQ ID NO: 1, that is induced by apoptosis. This is not considered to provide support such that applicants are considered to be in possession methods drawn to using the genus of eIF-5A molecules that are *apoptosis-induced*, because one could not immediately envision the

genus of apoptosis-induced eIF-5A molecules from the disclosure of only one apoptosis-induced eIF-5A, particularly in the complete absence of any teaching by way of structure what it is that actually confers the apoptotic-induction of eIF-5A. The genus is not immediately envisioned because A) the genus of any eIF-5A molecule is large, as pointed out by applicants, encompassing but not limited to cDNAs cloned from various eukaryotes including yeast, rat, chick embryo, alfalfa, rubber tree, and tomato plants (instant specification, page 5), and B) the genus is variable and includes eIF-5A transcripts whose suppression is suggested to actually induce apoptosis, in contradiction to the inhibition of apoptosis as claimed by applicants (see title and abstract of Tome et al., of record). The single transcript of SEQ ID NO: 1 is not considered to provide adequate support for methods of using a genus of molecules that is both large and varied.

Moreover, applicants claim language is drawn to methods of using a genus of eIF-5A molecules which are further identified by the functional language "apoptosis-induced". Neither applicants specification nor the prior art actually disclose any correlation between the structure of the instant eIF-5A of SEQ ID NO: 1, and the claimed function of being apoptosis-induced. Put simply, one of skill in the art would be unable to discern from either applicants specification or the prior art what it is that makes applicants' eIF-5A transcript apoptosis-inhibiting (as claimed), while another eIF-5A transcript is apoptosis-inducing (as taught by Tome et al.). Thus, because the distinguishing characteristics of the claimed genus are not described, claims to using the genus essentially amount to an invitation to experimentation to find other eIF-5A sequences which are apoptosis-induced, because one of skill in the art would not be apprised as what structural features of eIF-5A provide for its apoptotic induction.

Finally, the language drawn to "any agent" is not considered to have sufficient support, because the genus of inhibitors is very broad, and applicants have not disclosed a representative sample of agents which may act as inhibitors of activation of apoptosis induced eIF-5A. The genus of agents which may interfere with the activation of apoptosis induced eIF-5A is broadly drawn to include any antibody, antisense, ribozyme, triple helix, any protein or protein fragment that may regulate the target, or any small organic molecule inhibitor. In contrast, applicants have disclosed only 5 species of the genus of polyamines. There is no apparent disclosure of any small molecule inhibitor or antibody, or ribozyme, or protein or protein fragment that would act as an agent to inhibit the activation of apoptosis induced eIF-5A. Thus, the disclosure of methods utilizing a few species from the genus of polyamines is not considered to be representative of the claimed breadth of any agent that may interfere with the activation of apoptosis induced eIF-5A.

Accordingly, the specification does not provide adequate written description of the claimed genus any agents directed to the inhibition of any apoptosis-induced eIF-5A molecules.

5. Claims 1, 11, 87, and 88 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is repeated for the same reasons of record as set forth in the Office action mailed November 6, 2002. Additionally, a new basis for rejection for lack of enablement is set forth immediately

below, particularly drawn to the claimed role of eIF-5A in inhibiting or delaying apoptosis in any cell type.

To be clear, there are two distinct bases for the instant rejection. One was first set forth in the Office action mailed November 6, 2002, and is drawn to the practice of the claimed method steps in an *in vivo* environment. Applicants arguments directed to this are addressed towards the end of this section. A new basis for rejection follows immediately below, and is based on the lack of enablement of the claimed mechanism of reducing activated apoptosis induced eIF-5A, particularly as it relates to the outcome of reducing apoptosis *in any cell type.*

At the outset, it is noted that applicants have amended claim 1, and added new claims 87-89. Applicants contend that claims 1 and 88 are considered to be enabled as they relate to the *in vivo* practice of the instant methods. This is not adopted in regards to either claim, because claim 1 which specifically recites the method *in vitro*, is still drawn to practicing the method in any cell, which is not considered enabled for the reasons set forth below. In regards to claim 88, said claim still recites any mammalian cell and is thus still drawn to the practice of the method *in vitro* and *in vivo*. Only claim 89 is considered to be fully enabled, in light of the new basis of rejection for lacking enablement as described below.

The pending claims 1, 11, 87 and 88 are drawn to methods of delaying apoptosis in a cell, comprising administering an agent that reduces activation of apoptosis induced eIF-5A, wherein said reduction results in delaying apoptosis.

The specification as filed does not provide sufficient guidance or appropriate examples that would enable a skilled artisan to practice the method of using an agent to reduce activated eIF-5A to inhibit apoptosis in any cell type, because the specification has not established a nexus

between the reduction of eIF-5A and a reduction in apoptosis in any cell other than those of the corpus luteum, and further because the assertion that a reduction in activated eIF-5A leads to a reduction in apoptosis directly contradicts published reports of the relationship between activated eIF-5A and apoptosis. The prior art actually shows that reducing activated eIF-5A leads to in increase in apoptosis.

Thus, although the specification prophetically considers and discloses general methodologies and of reducing the level of activated eIF-5A to achieve a reduction of apoptosis, such a disclosure would not be considered enabling since the specification has not clearly established the existence of this mechanism, and because the prior art teaches results that contradict this claimed mechanism.

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Regarding the breadth of the claims and the nature of the invention, it is noted that the claimed reduction in the levels of activated eIF-5A is specifically recited for the purpose of reducing apoptosis-induced eIF-5A, which applicants allege is a different eIF-5A isoform than those of the prior art. In response, applicants attention is directed to the written description rejection above which sets forth that one of skill would not be able to envision any difference between the functionally identified "apoptosis-induced" version of eIF-5A and the structurally identified eIF-5A transcripts taught by numerous previous investigators. The written description

rejection is essentially due to the fact that applicants have not pointed to any structural features of their instant transcript that imparts the claimed functional activity of being "apoptosis-induced". Because applicants have only provided a functional description of their eIF-5A transcript (i.e. it is apoptosis induced) with no correlation to key structures that impart this quality, one of skill would be unable to use the instant specification to distinguish which eIF-5A transcripts are apoptosis-induced, and which are not. Accordingly, the term "apoptosis-induced" is given little patentable weight in using it to distinguish the instant eIF-5A from the eIF-5A of the prior art.

While applicants assert that the instantly claimed apoptosis-induced eIF-5A actually refers to a transcript termed eIF-5A2, applicants are reminded that the claim language does not reflect this. Rather, the claim language is drawn to any eIF-5A, particularly since the term "apoptosis-induced" is given little patentable weight as discussed above. The reference of Tome et al., which also centers on eIF-5A, is considered to speak to the state of the prior art regarding the enablement rejection of the instant invention.

Tome et al. teaches that "Excess Putrescine Accumulation Inhibits the Formation of Modified Eukaryotic Initiation Factor 5A (eIF-5A) and Induces Apoptosis" (See title). Since excess putrescine (i.e. a polyamine) actually induced apoptosis, which stands in contrast to the instantly claimed effect of reducing apoptosis, the mechanism claimed by applicant appears at the minimum to be unpredictable.

In further support of the contrast between applicants claimed result and that shown by the prior art, the reference of Pfeffer is provided. Pfeffer teaches that reduction of polyamines causes inhibits apoptosis, again contradicting the instantly claimed method of adding polyamines to

cells to reduce apoptosis; specifically, both clearly demonstrate that levels of polyamines vary in accordance with apoptosis.. These two references teach the same or related method steps, yet the outcome directly contradicts the instantly claimed result. Thus, the prior art is considered to be unpredictable with regard to polyamine-mediated reduction of apoptosis.

Since one of skill would understand from the teachings of the prior art that apoptosis varies positively with the levels of cellular polyamine, one of skill would not be able to rely upon the prior art at all in making and using the instant invention which claims to manipulate polyamine levels to inversely effect the occurrence of apoptosis. One of skill would consider the teachings of the prior art to be counter to the claimed results, and would therefore need to rely solely upon the teachings of the specification for guidance in practicing the claimed invention. However, the specification does not provide the requisite guidance for the practice of the claimed invention over the scope claimed, which includes inhibiting apoptosis in any cell type.

The specification teaches that by inducing superovulation in rats and later injecting prostoglandins to stimulate apoptosis, that apoptosis was non-existent in oocytes untreated with prostaglandin, and was lower among oocytes exposed to two doses of spermadine compared to oocytes exposed to only one dose of spermadine. No prostaglandin-only control is presented, and no statistics are shown, only a statement that apoptosis was lower in the oocytes treated with two doses of spermadine. Without the no prostaglandin control, and without any statistics, this is not very convincing evidence that it works in cells of the corpus luteum, let alone in any cell as claimed. This most clearly demonstrates that prostaglandins are capable of inducing apoptosis, but this is not the effect that is being claimed.

The specification also teaches that oocytes treated with spermadine, whether or not the cells were pretreated with prostaglandins, have reduced end-labeling characteristic of apoptosis. Although again no statistics have been presented, this is considered good evidence that spermadine does act to inhibit apoptosis in oocytes destined to become cells of the corpus luteum. However, this effect is not considered to be representative of any cells in light of the art cited above. Therefore, claim 89, the only claim that recites administration of spermadine to corpal luteum cells, is considered to be enabled.

In regards to the remaining claims, in order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of cells that behave similarly to those of the corpus luteum. In the absence of any real guidance from the specification, one would have to engage in undue trial and error experimentation, with no reasonably predictive chance that one would be able to practice the invention over the scope claimed.

Applicants have also argued against the enablement rejection drawn to the practice of the claimed methods *in vivo*. Specifically, the rejection of record stated that the instant specification does not enable the practice of the instant method claims *in vivo*. New claim 89 is considered to be enabled however, because the teachings of the specification show that spermadine injected into rats does inhibit apoptosis.

Insofar as applicants' arguments pertain to the remaining claims, applicants have argued that the examiner relies solely on the unpredictable state of art prior to the present invention, while ignoring the teachings of the present application.

Specifically, applicants acknowledge that it is known that polyamines given at a high dose can be toxic to cells and thus cause cell death, but that the specification thus teaches the administration of a polyamine to inhibit apoptosis.

In response, it is agreed that the specification teaches how administer spermidine to an *in vivo* whole animal system for inhibiting apoptosis in cells of the corpus luteum. At issue is the breadth pertaining to the cell-types in which apoptosis is being inhibited. It is maintained, based on the teachings of both the specification and the prior art, that the claimed methods will work predictably only in the cell-types in which such inhibition has been shown, that is, the corpus luteum. Clearly, the prior art as cited above teaches that in liver and epithelial cell lines, that polyamine levels and apoptosis vary in concert with one another, as opposed to applicants claimed results. As pointed out by applicants, "If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art." (Response, page 9). Since predictability and claim scope is an important consideration in the analysis of enablement, and because the instant invention is not considered to work in a wide variety of cell types as shown in the cited art, it is reasonable to limit the scope of the claimed invention to those cells for which a positive effect has been shown.

Applicants argue that sufficient guidance is given, because the claims require that the polyamine is administered at levels not to be toxic, and the specification provides guidance as to what constitutes toxic levels. Applicants point out that the specification provides the dosage of

spermadine per body weight needed to inhibit apoptosis. Thus, one skilled in the art would be able to use the provided rat data and apply it to other animal models and other cell types without undue experimentation. This is not considered convincing, because the cited art directly contradicts the claimed result of applicants invention. In light of the art teaching the opposite of that claimed by applicants, it is irrelevant that the application discloses the dosage needed to avoid toxicity, because there is no evidence the invention would in any way outside the cell types disclosed by applicants (i.e. the corpus luteum)

Applicants argue that the specification demonstrates that there is a correlation between in vitro and in vivo data, because example 5 provides data where apoptosis is inhibited in rat corpus luteum cells *in vitro* by treatment with a polyamine, while in example 6, it is shown that the same polyamine inhibits apoptosis when administered to a rat *in vivo*. This is not considered convincing, because as pointed out above, the *in vitro* data cannot be interpreted as supplied. With no statistical analysis, with no control in the *in vitro* study showing that the spermadine was not actually causing some of the apoptosis as seen in the prior art, the correlation applicants point to amounts to little more than a mere assertion that such a correlation exists. As such, one of skill would be forced to resort to undue trial and error experimentation to practice the method *in vivo* as claimed.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 87 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is drawn to a method for inhibiting apoptosis comprising administering an agent, wherein the agent is selected from the group consisting of spermadine, 1,3 Diamino-propane, 1,4 Diamino-butane, 1,7 Diamino-heptane, and 1,8 Diamino-octane, wherein said agent reduces an apoptosis cascade by transferring a 4-aminobutyl residue from spermadine to a residue on an inactive apoptosis-induced eIF-5A.

Applicants have claimed a method comprising administering an agent, wherein said agent may be chosen from 5 species of polyamines. However, the claim goes on to recite functional language whereby one polyamine, spermadine, serves as a substrate for the transfer of a residue from spermadine to eIF-5A. Thus the claim appears to assume that spermadine is the species of polyamine to be administered. If the spermadine is endogenous and the five species of polyamine to be administered are exogenous, clarification to this effect would obviate this rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Douglas Schultz whose telephone number is 571-272-0763. The examiner can normally be reached on 8:00-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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1635